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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,211	02/13/2004	Markku Anttila	13601-072	2487

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
06/04/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,211	ANTTILA, MARKKU	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/30/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 7-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 7-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/30/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment and argument

1. The response filed on **4/30/10** has been entered.

2. The response filed on **4/30/10** has been fully considered but they are not deemed to be persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1, 3-5 and 7-20 are pending in this action. Claims 1, 10, 12, 14, 16 and 19 are currently amended.

5. The information disclosure statement (IDS) submitted on 4/30/10 is acknowledged and has been reviewed.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-5 and 7-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Anttila (1997) in view of DEGregorio et al. (US 5,750,576) and Huebner et al (US 6,387,920) as evidence by Kangas (1990) for the reasons made of record in Paper no. 20091203 and as follows.

Applicant argues that the Examiner made several factual and or technical errors that appear to negatively influence the patentability analysis.

(i) Anttila discloses administering 60 mg tablets of toremifene. There is no mention of administering metabolites of toremifene. Blood levels of a major metabolite of toremifene, namely N-demethyltoremifene (or desmethyltoremifene), were measured, but no metabolite was administered.

(ii) Administration of a drug that metabolites to the active form in vivo is the same as administering the metabolite.

(iii) Food would inherently enhance bioavailability of toremifene.

(iv) It would have been obvious to substitute one SERM drug for another.

In response contrary to Applicant's assertion that (i) Anttila fails to disclose the administration of 60 mg/day, Anttila specifically teach administering a single 60 mg dose

of toremifene a metabolite ospemifene once after a 14 hour fasting (i.e., once daily) or once following a standard high fat meal) wherein once is considered once day and is administered after a meal (i.e., after intake of food stuff) as required.

Toremifene is a metabolite of ospemifene as earlier made of record in office action paper no. 20081201, wherein Kangas was used as an evidence to show that metabolites of toremifene result in ospemifene (i.e., TORE VI, see page 9, Fig. I). *In arguendo* DEGregorio et al. teach administering orally 5-100 mg /day of ospemifene for the treatment of osteoporosis (i.e., as it relates to claims 7, 10-13 and 16-20 (see abstract, col. 3, lines 1-10 and 59-64)). Applicant should note that this a rejection under 35 USC 103 and not under 35 USC 102. Therefore a prima facie case of obviousness has been met.

(ii) Applicant argues that the administration of a drug that metabolizes to the active form in vivo is only true in the case of prodrugs but not true for the case of toremifene. This again is found not persuasive because the art recognizes that toremifene metabolizes to ospemifene when administered. In arguendo DEGregorio et al teach ospemifene (having the same core structures as already made of record) and thus one of ordinary skill in the art would have been motivated to substitute Anttila's toremifene with DEGregorio's ospemifene with a reasonable expectation of success because there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved, consistent with the court in KSR.

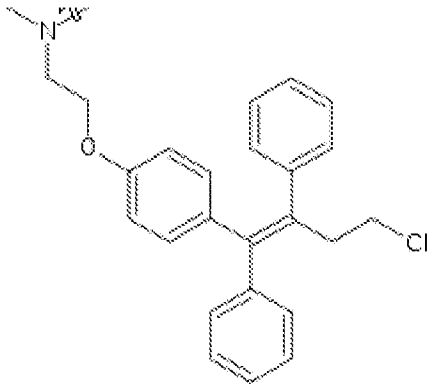
(iii) Applicant argues that Anttila's toremifene works equally well with or without administration of food and Anttila is teaching away.

Again this is found not persuasive because Anttila teaches administering the drug (in a tablet form, i.e., orally) after meal (meals have nutritional value) and therefore Anittila's method intrinsically would enhance the bioavailability of the compound.

(iv) Applicant argues that toremifene is an approved therapy for breast cancer and raloxifene is a indicated for treatment of osteoporosis. This again is found unpersuasive because Huebner et al teach treating osteoporosis, skin or vaginal atrophy with estrogen receptor modulators that may be in combination with toremifene (as required by instant claims 7-9, 15 and 18, see abstract, col. 35, lines 6-7,and col. 37, lines 20-21). Thus a prima facie case of obviousness has been established by the Examiner.

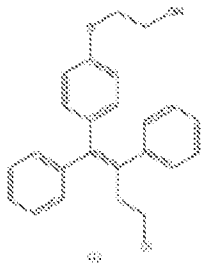
In Summary

Anttila discloses administering 60 mg/day of a metabolite toremifene



Toremifene

to healthy male volunteers that is structurally similar to

ospemifene  administered orally during or after meal (food) and therefore reasonably meets the limitation of claims 1 because food would have nutritional value and would reasonably inherently cause secretion of bile acids, and inherently enhance bioavailability of toremifene. Anttila teaches the food is taken "during, after or at a certain time interval to meals" (see introduction as required by instant claims 1 and 14).

Kangas is used to show that metabolites of toremifene result in ospemifene TORE III. See page 9, Fig. I. Therefore Administration of a drug that metabolizes to the active form in vivo is the same as administering the metabolite (i.e., ospemifene (TORE III), see Kangas, page 9, Fig. I) and as claimed.

With regards to instant claims 10-13, 16-17 and 19-20, Antilla teaches that toremifene (i.e., structurally similar to ospemifene) is administered at a dose of 60 mg per day (see sec. under methodology).

However, Anttila does not teach treating osteoporosis, skin atrophy or urinary symptoms, nor does Anttila teach that the compound is ospemifene (as required by instant claims 1, 7-9, 14-15). Anttila is also silent at what intervals ospemifene should be taken (as required by instant claims 3-5).

For this reason DEGregorio et al. is introduced.

DEGregorio et al. teaches ospemifene (see abstract), as required by instant claims 1-2, 7, 10 and 12. DEGregorio et al. further teaches administering orally 5-100 mg mg/day of ospemifene for the treatment of osteoporosis as (i.e., as it relates to claims 7, 10-13 and 16-20 (see abstract, col. 3, lines 1-10 and 59-64)).

However, DEGregorio et al. does not teach the administration of the drug with a meal, nor does DEGregorio et al. teach skin or vaginal atrophy or urinary symptoms. Although DEGregorio et al. fail to teach treating vaginal atrophy, DEGregorio et al. teach the use of these compounds in the treatment of estrogen replacement in postmenopausal women (see col. 1, lines 15-19).

Huebner et al teach the use estrogen receptor modulators in combination with a SERM drug toremifene for the treatment of osteoporosis, skin or vaginal atrophy (as required by instant claims 7-9, 15 and 18, see abstract, col. 35, lines6-7 and col. 37, lines 20-21). Again it has been shown that toremifene may be used for treating vaginal atrophy.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to expand the teachings of Anttila by substituting the drug of Antilla with DEGregorio et al. because, as evidenced by Kangas, toremifene a SERM drug that is a metabolite of ospemifene. Thus would have been obvious to one of ordinary skill in the art to substitute one SERM drug for another i.e., substitute toremifene for ospemifene and treat patients suffering from osteoporosis as taught by DEGregorio et al. with a reasonable expectation of success because the class of drugs are known SERM drugs which have been known in the art for treating osteoporosis.

Also, one of ordinary skill in the art would have employed the teachings of Antila and expanded the administration of the drug to include metabolites of toremifene, such as ospemifene as taught by DEGregorio et al. In summary, one of ordinary skill in the art would have been motivated to combine the teachings of Antila with that of DEGregorio et al. and Huebner et al. to include administration of toremifene and/or ospemifene for the treatment of osteoporosis and skin atrophy because DEGregorio et al. and Huebner et al. teach that toremifene (i.e., structurally similar to ospemifene) can be administered to treat the varying disorders such as osteoporosis and skin or vaginal atrophy. Based on the teaching of Anttila "that findings may help precision of administration instructions (e.g. administration during or after meals, or at a certain time interval to meals) are well known in the art and are routinely practiced", the varying point of administering the drug ospemifene (such as 2 hours, one hour, 0.5 hour) after starting the food intake is obvious to be optimized in order to find the most effective time interval for administration, as taught by Anttila (see introduction).

It should be noted that although in this rejection these prior arts of record are not indicated, Vasu, FDA (CDER) and Melander (all of record) have been used in prior rejections (e.g., see Paper No. 20080430) to show that the administration of drugs at different hours prior to and after food is well known in the art, and therefore obvious to perform.

Careful thought have been given to the remarks, but are found unpersuasive and the rejection is maintained as in the office action on record.

7. Claims 1, 3-5 and 7-20 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-6, 10 and 13-28 of U.S. Patent Application No. 11/201098 for the reasons made of record in Paper no. 20091203 and as follows.

Applicant argues that "one of ordinary skill in the art had no expectation that administering ospemifene slightly before, during or after food intake would have such a dramatic positive effect on the oral bioavailability of the drug".

In response the double patenting rejection is maintained for the same reasons that the 103 rejection is maintained. In this instance the allegation that the teaching of Anttila is away from claimed invention is not persuasive, because as evident by Melander et al, it would have been obvious to one of ordinary skill in the art to check the bioavailability of food effect on drugs before administration. As evident by Vasu, drugs are known in the art to be commonly administered with food or without food. With regard to Applicant's argument that the disclosure is directed to enhancing bioavailability and not treating urinary symptoms, there is no distinguishing step that indicates that once the drug is administered it would not treat urinary symptoms. Likewise Applicant's argument that the disclosure is to enhancing bioavailability and not to treating atrophy, because as soon as the drug is available, treating will proceed.

Also copending application recites treating urinary symptoms by the administration of the same drug in the same dosage amounts (see claim 1 of the copending application '098) and instant claims recite treating urinary symptoms as well (see instant claim 9, '211).

Careful thought have been given to the remarks, but are found unpersuasive and the rejection is maintained as in the office action on record.

8. Claims 1, 3-5 and 7-20 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of (U.S. Patent No. 6,984,665) for the reasons made of record in Paper no. 20091203 and as follows.

Applicant argues that "Applicant agrees that it is known that drugs are administered with food, but one would not have known the effect of co-administering food under the claimed conditions".

In response, this is found not persuasive because once the drug gets in the system it is available to proceed with said treatment. It would have been reasonable to expect an efficacious treatment modality would occur following "enhanced" bioavailability of the compound –ospemifene.

It should be noted that the claims of the patent '665 are drawn to a method for the treatment of urinary symptoms related to urogenital atrophy in women, or to administering effective amounts of formula (I), (i.e., ospemifene).

The "665 patent differs from the claimed invention insofar as it fails to expressly claim a method of enhancing bioavailability. The '665 patent only sets forth a method of

treatment or prevention of urinary symptoms related to urogenital atrophy as noted above.

However, it is contended that a method for treatment skin of atrophy, or epithelial or mucosal atrophy using compound the formula (I), would inherently treat urogenital atrophy, as evidenced by the specification of the '665 patent. For example, the '665 patent defines the symptoms related to urogenital atrophy as urinary and vaginal symptoms (see page3, lines 57-60). Thus, treating a woman with symptoms related to a urogenital atrophy would inherently treat a woman with urinary symptoms when ospemifene is administered with or without food. Whether enhanced bioavailability is claimed or not does not change the property of the drug when administered.

Careful thought have been given to the remarks, but are found unpersuasive and the rejection is maintained as in the office action on record.

9. Claims 1, 3-5 and 7-20 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of US 6,245,819 for the reasons made of record in Paper no. 20091203 and as follows.

The instant claims (8 and 15) are drawn to a method of treatment of symptoms related to skin atrophy, or to treating epithelial or mucosal atrophy in women, comprising administering to the woman an effective amount of formula (I) which ospemifene… .

Affidavit

10. The affidavit submitted by Risto Lammintausta under 37 CFR 1.132 filed 4/30/10 is insufficient to overcome the rejection of claims 1, 3-5 and 7-20 based upon the rejection under 35 USC 103 as set forth in the last Office action because:

As discussed above Anttila teaches administering toremifene at a dose of 60 mg a day (structurally similar to ospemifene which metabolizes to ospemifene) with food or without food. The Examiner did not conclude that toremifene metabolizes to ospemifene the drug that is claimed (thus a prodrug). Therefore administering toremifene is like administering ospemifene. Nonetheless even if toremifene fails to metabolize to ospemifene, because DEGregorio et al. teach administering ospemifene, one of ordinary skill in the art would have been motivated to substitute the drug of Anttila to DEGregorio et al's. with a reasonable expectation of success that the drug of DEGregorio et al. would behave the same as the drug of Anttila because both drugs are structurally similar and would behave the same as already explained in para. 6 above.

Declarant further asserts that "ospemifene is a minor metabolite of toremifene which does not contribute to the effect of toremifene and its main metaboiite desmethyltoremifene as breast cancer treatment compounds. Ospemifene in therapeutic doses demonstrates a therapeutic profile to treat vaginal atrophy, an estrogen agonizing effect, which is an opposite effect versus that of toremifene antagonizing the estrogen effect also in the vaginal epithelium"

Appellant is arguing unrelated issues here and has failed to recognize that the rejection is under 35 USC 103. DEGregorio et al. teach the use of these compounds in

the treatment of estrogen replacement in postmenopausal women (see col. 1, lines 15-19) and Huebner et al. teach the use estrogen receptor modulators in combination with a SERM drug toremifene for the treatment of osteoporosis, skin or vaginal atrophy (as required by instant claims 7-9, 15 and 18, see abstract, col. 35, lines 6-7 and col. 37, lines 20-21). Again it has been shown that toremifene may be used for treating vaginal atrophy.

With regards to Appellant's assertion the teachings of Anttila, DeGregorio et al., Huebner et al., and Kangas, either alone or in combination, do not suggest that the bioavailability of orally administered ospemifene would be enhanced by co-administering the ospemifene with food is found not persuasive because naturally food is always consumed before or after medication and therefore reasonably would also intrinsically increase the bioavailability of the drug to achieve the desired effect.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/S. V. G./
Examiner, Art Unit 1618
05/25/10

/Robert C. Hayes/
Primary Examiner, Art Unit 1649